BY ELECTRONIC MAIL

November 5, 2015

National Center for Environmental Assessment
US Environmental Protection Agency
Two Potomac Yard
2733 South Crystal Drive
Arlington, Virginia 22202

Re: Recommendations and Nominations for the Advancing Systematic Review Workshop Scheduled for December 2015

Dear Workshop Organizers:

The Chemical Products and Technology Division (CPTD) of the American Chemistry Council includes a number of chemical- and issue-specific Panels that are impacted by assessments conducted under the Integrated Risk Information System (IRIS). As such, we have a keen interest in how the National Center for Environmental Assessment (NCEA) evaluates the quality and risk of bias of studies that it considers in developing quantitative assessments of potential health risks presented by exposure to chemicals reviewed under IRIS. We are encouraged that NCEA has scheduled the December workshop on advancing systematic review, but are concerned that the proposed scope of the workshop is too narrowly focused and fails to consider the considerable amount of work that has already been devoted to the topic in Europe and elsewhere.

CPTD echoes the comments submitted by ACC on behalf of the Center for Advancing Risk Assessment Science and Policy and by its own Formaldehyde Panel regarding suggested changes to the workshop format and content. In particular, we believe that the December workshop should include a discussion of systematic reviews conducted on specific chemicals to provide tangible examples for the workshop participants to examine and to use as a basis for identifying general principles. Since EPA's reference values are most often based on laboratory studies, the workshop also should include a focus on animal toxicity data.

In light of the importance of focusing on a few case studies examining animal data for specific chemicals, we recommend that the workshop include a discussion of the non-cancer health effects data for trichloroethylene (TCE). As you are aware, TCE has been the subject of a recent IRIS assessment that defines a discrete universe of studies for calculating reference values.[1] These

[1] ACC prepared its own systematic review of the 19 studies EPA identified as candidates for determining a reference concentration for TCE in comments submitted to the Agency for Toxic Substances and Disease

studies have been the subject of publicly available critical reviews, including a 2014 review by EPA scientists, that provide an excellent basis for discussion at the December workshop. I have attached a list of reviews of TCE data that we encourage NCEA to consider as candidates for discussion. Perhaps the most relevant of these reviews is the one conducted by Drs. Chris Saranko and Keith Tolson which assesses the risk of bias in a critical TCE study using the approach outlined for the IRIS assessment for inorganic arsenic.[2]

Thank you for the opportunity to provide input on the upcoming workshop on systematic review. We look forward to participating in the workshop and hope that NCEA is able to incorporate our recommendations into the final agenda. Please feel free to contact me at 202-249-6727 or srisotto@americanchemistry.com if you have any questions about these recommendations.

Sincerely,

Steve Risotto

Stephen P. Risotto
Senior Director

Registry (ATSDR) earlier this year. This review is available at http://www.regulations.gov/#!documentDetail;D=ATSDR-2014-0001-0011.

[2] Dr. Saranko can be contacted at csaranko@geosyntec.com.

Recent Systematic Reviews of Trichloroethylene Toxicity Data

Bukowski J. Critical review of the epidemiologic literature regarding the association between congenital heart defects and exposure to trichloroethylene. *Crit Rev Toxicol* 44(7):581-89 (2014).

Hardin B *et al.* Trichloroethylene and dichloroethylene: a critical review of teratogenicity. *Birth Defects Res A Clin Mol Teratol* 73(12):931–955 (2005).

Tolson JK and Saranko CJ. Critical review of the EPA's weight-of-evidence analysis for fetal cardiac malformations following TCE exposure. Attachment to November 26, 2014 letter from the California Manufacturers & Technology Association to Dr. Kenneth Olden.

Watson RE *et al*. Trichloroethylene-contaminated drinking water and congenital heart defects: a critical analysis of the literature. *Reprod Toxicol* 21(2):117–147 (2006).

US EPA. TCE developmental cardiac toxicity assessment update. Document ID EPA-HQ-OPPT-2012-0723-0045. Included in public docket for the Office of Pollution Prevention and Toxics chemical risk assessment for TCE for the Work Plan Program under the Toxic Substances Control Act (Undated, added to public docket in July 2014). Available at http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPPT-2012-0723-0045.

November 5, 2015

USEPA
National Center for Environmental Assessment

Submitted electronically to: EPA_Sys-Review@icfi.com

Re: Recommendations for Topics and Speakers for EPA's December 16-17, 2015 "Advancing Systematic Review" Workshop

Dear Workshop Organizers:

The Center for Advancing Risk Assessment Science and Policy (ARASP),[1] which is managed by the American Chemistry Council (ACC)[2], welcomes the opportunity to provide input as EPA's National Center for Environmental Assessment (NCEA) plans its December 16-17, 2015 Systematic Review workshop. Incorporation of systematic review practices into the IRIS program is critical for improving the transparency, quality, and timeliness of IRIS assessments. Below we provide some recommendations and suggestions to strengthen the workshop.

1. The Workshop Should Focus Primarily on Implementing Approaches to Judge the Quality of Animal Toxicology Data

The majority of information available and relied upon in IRIS assessments is animal toxicology data. Therefore evaluating the quality (including risk of bias) of these data should be the highest priority for the IRIS program and this workshop. The Klimisch approach has been used by regulatory agencies in Europe, as well as OECD, since the mid 1990's indicating widespread support of this method by chemical evaluation and regulatory programs of the more than 30 countries that are OECD members, including the U.S. It is unclear why the IRIS program has not yet adopted this approach, or at least pieces of the approach, and instead the program continues to use unclear and inconsistent criteria for this

[1] ARASP is a coalition of twenty-two organizations focused on promoting the development and application of up-to-date, scientifically sound methods for conducting chemical assessments. More information on ARASP can be found: http://arasp.americanchemistry.com/

[2] The American Chemistry Council (ACC) represents the leading companies engaged in the business of chemistry. ACC members apply the science of chemistry to make innovative products and services that make people's lives better, healthier and safer. ACC is committed to improved environmental, health and safety performance through Responsible Care®, common sense advocacy designed to address major public policy issues, and health and environmental research and product testing.

important data stream. If EPA believes that important Risk of Bias (RoB) elements need to be included, then this workshop should provide an opportunity for a clear and focused discussion about 1) the utility and applicability of the Klimisch approach and 2) what modifications may be needed to enable it to be used confidently within EPA chemical evaluation programs.

We provide the following recommendations for speakers and topics to help EPA move forward with transparent quality criteria to evaluate this evidence stream:

- Include experts from ECHA and the REACH program that have been using Klimisch for regulatory purposes. For example, ECHA staff implementing ECHA guidance on evaluating available information[3] would be helpful participants. Industry experts who have been working to provide this information to ECHA as part of chemical specific dossiers submitted under REACH would also provide great value. In particular, we recommend Nicholas Ball from Dow Chemical in Europe.[4]

- Experts from the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) have expanded the Klimisch justification phrases using alphanumeric scores for each reliability category and ECETOC has employed these within its Joint Assessment of Commodity Chemicals program.[5] ECETOC experts with experience using this expanded Klimisch scoring system, therefore, would also bring great value added to this workshop; we recommend Dr. Jim Bridges or Dr. Mark Pemberton.[6]

- Include experts from the OECD who worked on the OECD High Production Volume (HPV) Chemicals Programme where the Klimisch approach was used to ensure that there is sufficient good quality information on each of the elements that make up the Screening Information Data Set (SIDS).[7]

- Include experts from EPA who have evaluated the ToxRTool's ability to rate the reliability of toxicological data.[8] In their publication, these EPA scientists concluded "ratings were most consistent for high-quality journal articles, but less consistent as study quality decreased." These authors went on to suggest the need for specific refinements and the workshop provides a perfect opportunity for further discussion with the EPA staff who have conducted this important evaluation.

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[3] See 2001 ECHA Guidance on information requirements and chemical safety assessment, Chapter R.4: Evaluation of available information. Available at: https://echa.europa.eu/documents/10162/13643/information_requirements_r4_en.pdf.
[4] Nicholas Ball can be reached at: nball@dow.com.
[5] See for example Appendix A Criteria For Reliability Categories available at: http://members.ecetoc.org/Documents/Document/JACC%20051.pdf
[6] Dr. Bridges can be reached at j.bridges@surrey.ac.uk and Dr. Pemberton can be reached at markpemberton@systox.com.
[7] See OECD HPV Evaluation Guide available at: http://www.oecd.org/chemicalsafety/risk-assessment/36045203.pdf.
[8] See Segal D, Makris SL, Kraft AD, Bale AS, Fox J, Gilbert M, Bergfelt DR, Raffaele KC, Blain RB, Fedak KM, Selgrade MK, Crofton KM. Evaluation of the ToxRTool's ability to rate the reliability of toxicological data for human health hazard assessments. Regul Toxicol Pharmacol. 2015 Jun;72(1):94-101. doi: 10.1016/j.yrtph.2015.03.005. Epub 2015 Mar 14.

- Include EPA experts that worked to develop EPA's draft Development Materials for the IRIS review of Inorganic Arsenic. In April 2014, IRIS staff provided draft documents that included a RoB evaluation of animal data for inorganic arsenic. Public comments were provided to EPA on these draft documents; however, EPA has not yet responded to these comments. It would be useful to hear from this assessment team the lessons they have learned from the approach, what, if any, remaining concerns they have, and how they are currently considering implementing it in the future.

- Include experts that have been working to develop scoring tools for non-guideline animal toxicology studies. ARASP has been working with experts at Ramboll Environ who have given much thought to quantitative and qualitative evaluation tools for evaluating guideline and non-guideline studies. We recommend including Dr. Robinan Gentry[9] in these discussions.

2. The Focus on the ACROBAT-NSRI Approach is Overemphasized

As most IRIS data are animal evidence, it is unclear why EPA is using the ACROBAT-NSRI tool as a starting point to evaluate methods. Even if the focus were just on epidemiologic data, a tool designed to evaluate non-randomized studies of intervention does not appear to be the best starting point. Although adoption of a tool designed to evaluate clinical epidemiology to environmental/occupational epidemiology is possible, it is likely to be of low value and utility. The document presumes an understanding of clinical terminology and a fairly advanced knowledge of methods and clinical research which is not necessary for IRIS-type datasets. We recommend speakers and topics that have worked on the following projects:

- Include experts knowledgeable in approaches for evaluating human data and environmental exposures. We recommend authors of the following approaches:

    - Money CD, Tomenson JA, Penman MG, Boogaard PJ, Lewis RJ. A systematic approach for evaluating and scoring human data. Regul Toxicol Pharmacol. 2013 Jul;66(2):241-7.[10]
    - Prueitt RL, Lynch HN, Zu K, Sax SN, Venditti FJ, Goodman JE. Weight-of-evidence evaluation of long-term ozone exposure and cardiovascular effects. Crit Rev Toxicol. 2014 Oct;44(9):791-822.[11]

- Include experts who can speak broadly to the adoption of approaches and tools that may be best for the types of data available for environmental chemicals. We recommend Dr. Douglas Weed[12].

[9] Dr. Gentry can be reached at rgentry@ramboll.com.
[10] Dr. Money can be reached at chrismoneyuk@gmail.com.
[11] Dr. Prueitt can be reached at rprueitt@gradientcorp.com.

3. The Workshop Should Focus on Specific, Publicly Available Examples

Rather than talking in theory or generically, we believe this workshop would benefit from using case studies and specific examples. All this information should be made publicly available at least 30 days in advance of the workshop. Examples currently exist for systematic reviews or pieces of systematic reviews for environmental chemicals and much can be learned by examining these reviews as case studies. In addition to our suggestion to evaluate the IRIS inorganic arsenic documents, our understanding is that other groups are providing additional examples to EPA. We support a workshop that is focused around the examination of specific case studies.

Finally, EPA mentions using a model of "key characteristics of carcinogens" as an organizing principle for mechanistic data but neglected to provide any citations or documentation. To ensure full participation and robust dialogue, EPA should make all underlying information available to all workshop participants, with sufficient time for review, in advance of the workshop.

4. Evidence Integration Remains an Important Systematic Review Area for Discussion

EPA has not proposed any discussion on evidence integration. While this may likely be due to time constraints, the topic remains an important area in need of further discussion and deliberation among stakeholders. If scheduling allows, this topic should also be included.

- Include experts who have studied approaches for integrating evidence. We recommend authors of the following approaches:
    - Lavelle KS, Schnatter AR, Travis KZ, Swaen GMH, Pallapies D, Money C, Priem P, Vrijhof H. Framework for integrating human and animal data in chemical risk assessment. Reg Tox and Pharm 2012;62:302-312.[13]
    - Rhomberg LR, Bailey LA, Goodman JE. Hypothesis-based weight of evidence: A tool for evaluating and communicating uncertainties and inconsistencies in the large body of evidence in proposing a carcinogenic mode of action—naphthalene as an example. Critical Reviews in Toxicology 2010;40(8):671-696.[14]

Thank you in advance for your consideration of ARASP's comments. We look forward to participating in this important workshop and hope the final agenda will reflect our recommendations. If you have any

[12] Dr. Weed can be reached at douglaslweed@aol.com.
[13] Dr. Lavelle can be reached at: Karlene.s.lavelle@exxonmobil.com.
[14] Dr. Rhomberg can be reached at: lrhomberg@gradientcorp.com.

questions, or need clarification of our comments, please contact me at 202-249-6417 or nancy_beck@americanchemistry.com.

Sincerely,

Nancy B. Beck, PhD, DABT
American Chemistry Council (ACC)
Senior Director
Regulatory and Technical Affairs
On behalf of ARASP

ARASP members:
Acrylonitrile Group
American Cleaning Institute
American Composite Manufacturers Association
American Forest and Paper Association
American Petroleum Institute
CropLife America
Halogenated Solvents Industry Alliance
Nickel Producers Environmental Research Association
Styrene Information and Research Center
Wood Preservative Science Council
ACC Chlorine Chemistry Division
ACC Ethylene Oxide Panel
ACC Formaldehyde Panel
ACC Hexavalent Chromium Panel
ACC High Phthalates Panel
ACC Hydrocarbon Solvents Panel
ACC Olefins Panel
ACC Oxo Process
ACC Propylene Oxide/Propylene Glycol Panel
ACC Health, Products, and Science Policy Committee
ACC Silicones Environmental, Health and Safety Center of North America
ACC Vinyl Chloride Health Committee

cc:
Dr. Vince Cogliano, EPA
Dr. Ken Olden, EPA
Dr. Lynn Flowers, EPA
Dr. Thomas Burke, EPA
IRIS General Comments Docket, EPA-HQ-ORD-2014-0211

November 5, 2015

USEPA Headquarters
Ariel Rios Building
1200 Pennsylvania Avenue, N. W.
Washington, DC 20460

Submitted to EPA_Sys-Review@icfi.com

Re: Discussion Topics and Experts for December 2015 Advancing Systematic Review Workshop

Dear Sir or Madam:

On December 16 - 17, 2015, the EPA's National Center for Environmental Assessment (NCEA) will host a workshop on "Advancing Systematic Review for Chemical Risk Assessment" in Arlington, VA. The workshop seeks to examine developments and applications of methods for the identification and evaluation of different types of epidemiology, animal toxicology, and mechanistic evidence in chemical risk assessment. EPA is soliciting input on suggested scientific experts in systematic review and discussion topics for the workshop. The American Chemistry Council's Formaldehyde Panel appreciates this opportunity to provide input into the December workshop and offers the suggestions below for both (a) areas of discussion at the workshop and (b) specific experts who have previously published on the topic and can inform EPA's implementation of systematic review.

Workshop Discussion Areas

According to the EPA's webpage[1] the workshop will consist of two sessions:

1) From theory to practice: lessons learned from the evaluation of studies of chemical exposure. This session will use the assessment of risk of bias in non-randomized studies of interventions (ACROBAT-NRSI) as a starting point to examine developments in methods used to evaluate studies.
2) Systematic review relating to mechanistic data: what is really needed, and how can it be efficiently applied?

Although it is not entirely clear from the topics of the two sessions, the Panel believes that EPA should use these sessions to focus on two very important questions in the context of systematic review: (a) how the quality (including but not limited to risk of bias) and strength of a study within a given discipline, such as epidemiology, should be assessed; and (b) having assessed each study's quality, how the full set

[1] http://www2.epa.gov/iris/advancing-systematic-review-workshop-december-2015

of data *within* a particular discipline such as epidemiology should be evaluated and integrated to provide a coherent and balanced assessment.

If EPA were to examine either of these two questions, the Panel respectfully suggests that formaldehyde would make a good case study. Formaldehyde is a well-studied substance that has a robust volume of epidemiology, toxicology, and mechanistic data. EPA's ongoing assessment of formaldehyde will require EPA to form scientific judgments about the quality and strength of numerous mechanistic studies in order to determine whether any of those studies provide plausible evidence of a mechanism by which exposure to exogenous formaldehyde may result in acute myeloid leukemia. Specifically, EPA's assessment of formaldehyde would require the Agency to consider and integrate evidence across multiple peer-reviewed epidemiological studies and to synthesize disparate findings with respect to myeloid leukemia and especially acute myeloid leukemia. Unlike evaluations based on largely consistent evidence within and across lines of inquiry, greater demands are placed on the evaluation of substances, such as formaldehyde, where the evidence is ambiguous at best, and possibly contradictory. EPA's approach to both of these questions would provide a useful case study to explore the broader methodological issues raised by the workshop, and lead to stronger methodologies that would help elucidate other substances for which the evidence is not straightforward or clear.

Indeed, there have been several publications that have addressed the systematic review issues that form the basis for this workshop in the context of formaldehyde. Below we highlight three published articles that conduct systematic reviews to assess the strength and consistency of potential associations. These publications, and their authors, might assist EPA in further framing a formaldehyde case study for the workshop:

- Checkoway, Harvey, Paolo Boffetta, Diane J. Mundt, and Kenneth A. Mundt. "Critical review and synthesis of the epidemiologic evidence on formaldehyde exposure and risk of leukemia and other lymphohematopoietic malignancies." Cancer Causes & Control 23, no. 11 (2012): 1747-1766.
- Swenberg, James A., Benjamin C. Moeller, Kun Lu, Julia E. Rager, Rebecca C. Fry, and Thomas B. Starr. "Formaldehyde Carcinogenicity Research 30 Years and Counting for Mode of Action, Epidemiology, and Cancer Risk Assessment." Toxicologic pathology (2012): 0192623312466459.
- Rhomberg, Lorenz R., Lisa A. Bailey, Julie E. Goodman, Ali K. Hamade, and David Mayfield. "Is exposure to formaldehyde in air causally associated with leukemia?—A hypothesis-based weight-of-evidence analysis." Critical reviews in toxicology 41, no. 7 (2011): 555-621.

Additionally, we would recommend that EPA involve internationally renowned experts in epidemiology that in addition to having strength in critically reviewing and synthesizing epidemiological evidence, have conducted relevant research, such as Drs. David Coggon and Keith Palmer: Coggon, David, Georgia Ntani, E. Clare Harris, and Keith T. Palmer. "Upper Airway Cancer, Myeloid Leukemia, and Other Cancers in a Cohort of British Chemical Workers Exposed to Formaldehyde" Am. J. Epidemiol. first published online April 8, 2014 doi:10.1093/aje/kwu049

Workshop Experts

The Panel is aware of several scientists who have devoted substantial attention to the question of how systematic reviews should be conducted in the development of a chemical-specific risk assessment (apart from formaldehyde). We have endeavored to identify some of those scientists below, and suggest that these experts be considered as presenters or panelists during the workshop:

- Dr. George Maldonado of the University of Minnesota has conducted systematic evaluations of epidemiology and also reviewed impacts of individual vs. population based causal estimates. A few examples of his publications are included below:
    - Maldonado, George. "Toward a clearer understanding of causal concepts in epidemiology." Annals of epidemiology 23, no. 12 (2013): 743-749.
    - Lash, Timothy L., Matthew P. Fox, Richard F. MacLehose, George Maldonado, Lawrence C. McCandless, and Sander Greenland. "Good practices for quantitative bias analysis." International journal of epidemiology (2014): dyu149.
- Dr. Timothy Lash of Emory University has conducted several evaluations of epidemiology data and risk of bias. Some examples of those reviews are included below.
    - Lash, Timothy L., and Thomas P. Ahern. "Bias analysis to guide new data collection." The international journal of biostatistics 8, no. 2 (2012): 1-23.
    - Lash, Timothy L., Matthew P. Fox, and Aliza K. Fink. Applying quantitative bias analysis to epidemiologic data. Springer Science & Business Media, 2011.
- Drs. Julie Goodman and Lorenz Rhomberg of Gradient Corp have co-authored numerous publications focused on systematic review and weight of evidence frameworks for various substances and data endpoints. A few of their publications are listed below:
    - Rhomberg, Lorenz R., Julie E. Goodman, Lisa A. Bailey, Robyn L. Prueitt, Nancy B. Beck, Christopher Bevan, Michael Honeycutt et al. "A survey of frameworks for best practices in weight-of-evidence analyses." Critical reviews in toxicology 43, no. 9 (2013): 753-784.
    - Goodman, Julie E., Robyn L. Prueitt, Sonja N. Sax, Lisa A. Bailey, and Lorenz R. Rhomberg. "Evaluation of the causal framework used for setting National Ambient Air Quality Standards." Critical reviews in toxicology 43, no. 10 (2013): 829-849.
    - Prueitt, Robyn L., Julie E. Goodman, Lisa A. Bailey, and Lorenz R. Rhomberg. "Hypothesis-based weight-of-evidence evaluation of the neurodevelopmental effects of chlorpyrifos." Critical reviews in toxicology 41, no. 10 (2011): 822-903.
    - Goodman, Julie E., Raphael J. Witorsch, Ernest E. McConnell, I. Glenn Sipes, Tracey M. Slayton, Carrie J. Yu, Amber M. Franz, and Lorenz R. Rhomberg. "Weight-of-evidence evaluation of reproductive and developmental effects of low doses of bisphenol A." Critical reviews in toxicology 39, no. 1 (2009): 1-75.
- Dr. Chris Money has co-authored an approach for systematically evaluating and scoring human data. Additional details can be found in: Money, Chris D., John A. Tomenson, Michael G. Penman, Peter J. Boogaard, and R. Jeffrey Lewis. "A systematic approach for evaluating and scoring human data." Regulatory toxicology and pharmacology 66, no. 2 (2013): 241-247.

We appreciate EPA organizing this workshop on systematic review, which we see as a critical aspect of the IRIS process. We thank you for consideration of the suggestions noted above and feel free to contact me by phone (202-249-6707) or email (Kimberly_White@americanchemistry.com) with any questions.
Sincerely,

Kimberly Wise White, PhD
American Chemistry Council (ACC)
Senior Director
Chemical Products & Technology Division
On Behalf of the ACC Formaldehyde Panel